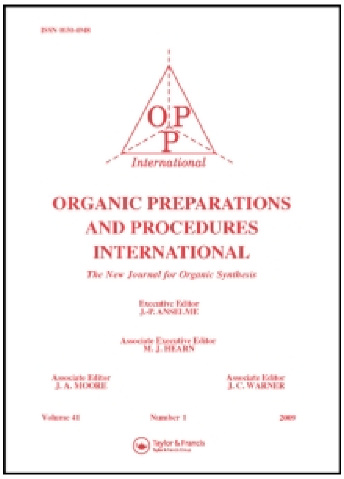

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A SIMPLE ONE-STEP SYNTHESIS OF 2-PYRIDONES FROM BENZYLIDENEACETOPHENONES

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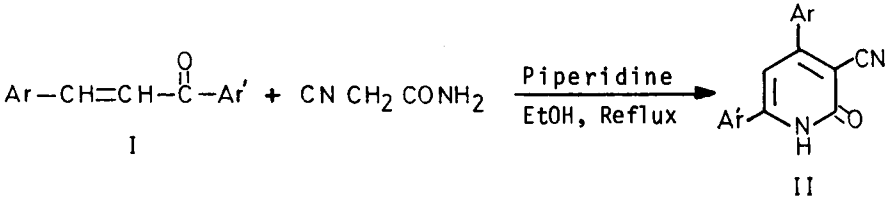
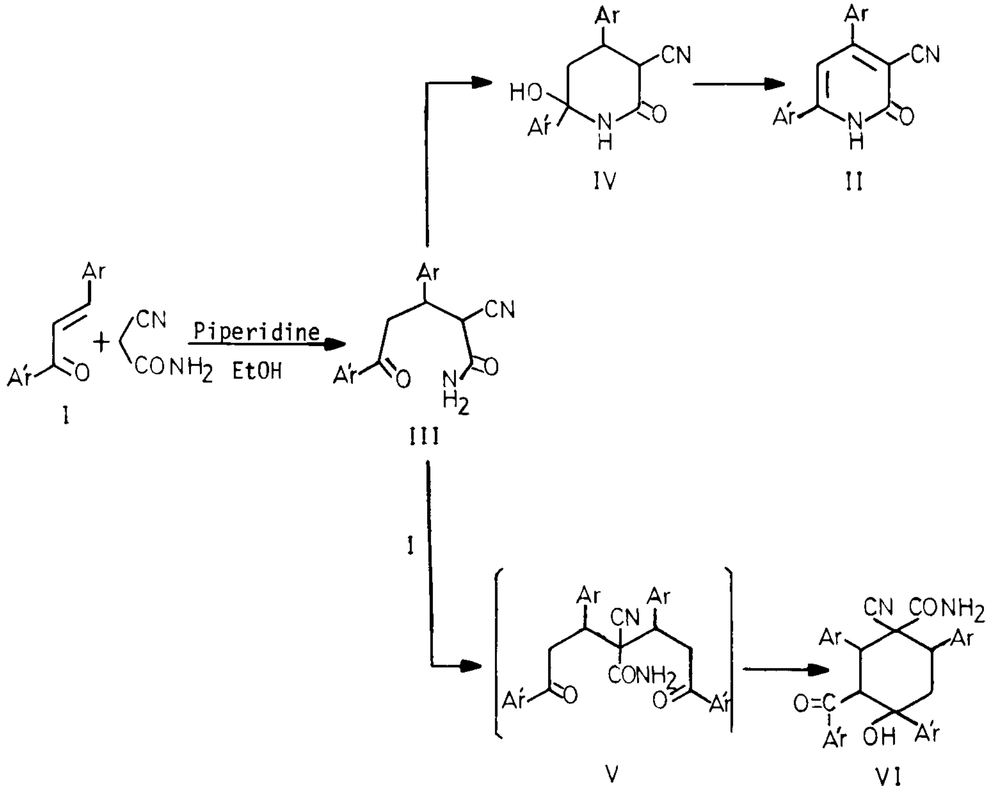
The study of the reaction of malonamide and cyanoacetamide with benzylideneacetophenone (chalcone) has lead to contradictory results and has been reported to yield either an unidentified compound,[1] the Michael adduct,[2] an unsaturated piperidone,[3] or mixtures of compounds.[4] We now report that under appropriate conditions the reaction of benzylideneacetophenones (I) with cyanoacetamide is a good route for the one-step synthesis of 4,6-diaryl-3-cyano-2-pyridones (II). The reaction involves the Michael addition of cyanoacetamide followed by spontaneous cyclization, dehydration and dehydrogenation.



The reaction is very simple to perform and pyridones II precipitate in good yield from the reaction mixture. The pyridones obtained from a series of substituted benzylideneacetophenones are listed in Table 1, together with the yields and physical data. With benzylideneacetophenones bearing nitro substituents (I, Ar=$\underline{m}$-$NO_2C_6H_4$, Ar'=C_6H_5 and Ar=C_6H_5, Ar'=$\underline{p}$-$NO_2C_6H_4$) the expected pyridones are not obtained from the complex reaction mixture.

The preparation of pyridones II can also be achieved by reaction of cyanoacetamide with benzylideneacetophenones at room temperature, but the yields are lower owing to the formation, together with pyridones II, of variable amounts of 3,5-diaryl-2-cyano-5-oxopentanamides (III) (Michael adducts) or 2-benzoyl-4-carboxamido-4-cyano-1,3,5-triarylcyclohexanols (VI) (Scheme 1). The later compounds result from the Michael addition of benzylideneacetophenone to III, giving rise to V followed by an aldol type cyclization to VI. 4'-Nitrobenzylideneacetophenone (I, Ar= C_6H_5, Ar'=p-$NO_2C_6H_4$) reacts with cyanoacetamide at room temperature to give 6-hydroxy-2-piperidone IV (Ar=C_6H_5, Ar'=p-$NO_2C_6H_4$) as the only product.



SCHEME 1

TABLE 1. Physical data of 4,6-diaryl-3-cyano-2-pyridones (II)[a]

Cmpd	Ar	Ar'	Time (hrs)	Yield	mp.[b] (°C)	Combustion Analysis C,H,N Calcd.(Found)
IIa	C_6H_5	C_6H_5	60	62	302-304	79.41 4.41 10.29 (79.08)(4.24)(10.15)
IIb	p-$CH_3C_6H_4$	C_6H_5	36	75	310-312	79.12 4.89 9.79 (78.85)(4.92)(10.16)
IIc	p-$CH_3OC_6H_4$	C_6H_5	24	78	306-308	75.49 4.63 9.27 (75.17)(4.73)(9.21)
IId	p-ClC_6H_4	C_6H_5	42	68	313-315	70.47 3.59 9.14[c] (70.86)(3.66)(9.40)
IIe	C_6H_5	p-$CH_3C_6H_4$	65	57	246-248	79.12 4.89 9.79 (78.95)(5.13)(9.94)
IIf	C_6H_5	p-$CH_3OC_6H_4$	70	58	254-256	75.49 4.63 9.27 (75.23)(4.81)(9.22)
IIg	C_6H_5	p-ClC_6H_4	70	51	288-290	70.47 3.59 9.14[d] (70.22)(3.81)(9.36

a) All compounds were recrystallized from ethanol. b)Melting points are uncorrected.

c) Cl: Calcd, 11.58. Found, 11.95. d) Cl: Calcd, 11.58. Found, 11.62

EXPERIMENTAL

Melting points were determined in capillary tubes. The NMR spectra were recorded on a Varian T-60A and IR spectra were measured with a Perkin-Elmer 257. Microanalysis were performed by Centro Nacional de Química Orgánica de Madrid. The reactions were monitored by TLC performed on silica gel plates with benzene/ethyl acetate1:1 as the eluent. Benzylideneacetophenone (Ia) was obtained from Merck, Ib-Ie were prepared as described[8]. The methods of Staudinger[9] and Dilthey[10] were used for the preparation of If and Ig. 3-Nitrobenzylideneacetophenone (Ih) and 4'-nitrobenzylideneacetophenone (Ii) were prepared as described by Sorge[11] and Weygand,[12] respectively.

4,6-Diaryl-3-cyano-2-pyridones (II). General Procedure.- The appropriate benzylideneacetophenone (I) (0.005 mole) and 0.005 mole of cyanoacetamide were mixed in 25 ml of dry ethanol and a few drops of piperidine added. The reaction mixture was heated to reflux for a variable number of hours (Table 1). The pyridones II precipitated as colorless crystalls on cooling and were collected. A further crop of product could be obtained by evaporation of the mother liquors. The combined crops were recrystallized from ethanol. The physical and analytical data of these compounds are collected in Table 1 and spectroscopic data in Table 2.

TABLE 2. Spectroscopic data of 4,6-diaryl-3-cyano-2-pyridones (II)

	NMR[a]				IR[b]	
Cmpd	ArH	5-H	CH_3-	CH_3O-	CN	CO
IIa	7.10-7.80	6.60			2220	1640
IIb	7.00-7.80	6.55	2.20		2215	1635
IIc	6.85-7.70	6.60		3.70	2215	1640
IId	7.20-7.80	6.60			2215	1635
IIe	7.00-7.80	6.60	2.25		2215	1635
IIf	6.75-7.80	6.60		3.75	2220	1630
IIg	7.10-7.80	6.55			2220	1640

a) Obtained in DMSO-d_6 at 60 MHz and reported in δ values against TMS as the internal standard.

b) Performed in potassium bromide pellets.

3-Phenyl-5-(p-methylphenyl)-2-cyano-5-oxopentanamide (IIIe).- To 1.1 g of 4'-methylbenzylideneacetophenone (Ie) (0.005 mole) and 0.42 g (0.005 mole) of cyanoacetamide in 25 ml of dry ethanol, a few drops of piperidine were added and the mixture is stirred at room temperature until complete solution occurred. After standing at room temperature, 0.54 g (46%) of IIIe, mp. 151-153° were collected and recrystallized from ethanol. Pyridone IIe was recovered from the mother liquors in 38% yield.

Anal. Calcd. for $C_{19}H_{18}N_2O_2$: C, 74.51; H, 5.88; N, 9.15. Found: C, 74.91; H, 5.99; N, 9.22.

IR (KBr pellet): 3450, 3320, 2240, 1675, 1650, 1600 cm^{-1}. NMR (DMSO-d_6): δ 7.10-7.90 (m, 9H arom, NH_2), 3.20-4.20 (m, 4H), 2.25 (s, 3H, CH_3).

3-Phenyl-5-(p-methoxyphenyl)-2-cyano-5-oxopentanamide (IIIf).- Following the procedure described above and starting from 1.19 g (0.005) mole of 4'-methoxybenzylideacetophenone (If) and 0.42 g of cyanoacetamide, 0.55 g (56%) of IIIf are isolated, mp.154-155°(from ethanol). Pyridone IIf is recovered in 37% yield from the mother liquors.

Anal. Calcd. for $C_{19}H_{18}N_2O_3$: C, 70.81; H, 5.59; N, 8.69. Found:

C, 70.86; H, 5.54; N, 8.88.

IR (KBr pellet): 3460, 3320, 2240, 1675, 1650, 1595 cm^{-1}. NMR ($DMSO-d_6$): δ 6.90-8.00 (m, 9H arom, NH_2), 3.20-4.30 (m, 4H), 3.80 (s, 3H, CH_3O).

2-Benzoyl-4-carboxamido-4-cyano-1-phenyl-3,5-di(p-methylphenyl)-cyclohexanol (VIb).- A suspension of 1.11 g (0.005 mole) of 4-methylbenzylideneacetophenone (Ib) and 0.42 g (0.005 mole) of cyanoacetamide in 25 ml of dry ethanol is stirred at room temperature with a few drops of piperidine until total solution of the reactants occurs. After standing at room temperature, 0.13g (9%) of VIb precipitated, were filtered and recrystallized from ethanol, mp. 221-223°. Concentration of the mother liquors affords 0.58 g (41%) of pyridone IIb.

Anal. Calcd. for $C_{35}H_{32}N_2O_3$: C, 79.54; H, 6.06; N, 5.30. Found: C, 79.29; H, 6.15; N, 5.37.

IR (KBr pellet): 3470, 3360, 3330, 2230, 1680, 1650 cm^{-1}. NMR ($DMSO-d_6$): δ 6.80-7.80 (m, 18H arom, NH_2), 6.45 (s, 1H, OH),3.00 -4.80 (m, 3H), 2.25 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 1.80 (d,2H CH_2). MS: m/e= 528 (M^+, 2), 307(3), 224(20), 223(100), 145(16), 120(16).

2-Benzoyl-4-carboxamido-4-cyano-1-phenyl-3,5-di-(p-chlorophenyl) cyclohexanol (VId).- Starting from 1.21 g of 4-chlorobenzylideneacetophenone (Id) and 0.42 g of cyanoacetamide and following the same procedure described above, 0.21 g (15%) of VId were isolated mp. 232-234°(from ethanol). Pyridone IId was isolated from the mother liquors in 40% yield.

Anal. Calcd. for $C_{33}H_{28}N_2O_3Cl$: C, 69.35; H, 4.90, N, 4.90; Cl, 12.43. Found: C, 69.67; H, 4.79; N, 5.35; Cl, 12.68.

IR (KBr pellet): 3440, 3360, 2230, 1685, 1650, 1645, 1605 cm^{-1} NMR ($DMSO-d_6$): δ 6.80-7.80 (m, 18H arom, NH_2), 5,70 (s, 1H, OH) , 3.30-4.60 (m, 3H), 2.00 (d, 2H, CH_2).

3-Cyano-4-phenyl-6-hydroxy-6-(p-nitrophenyl)-2-piperidone (IVi).- A suspension of 1.26 g (0.005 mole) of 4'-nitrobenzylideneacetophenone (Ii) and 0.42 g (0.005 mole) of cyanoacetamide in 20 ml of dry ethanol with a few drops of piperidine was stirred at room

temperature for a few hours. A solid precipitated before complete solution of the reactants was achieved. Filtration of the solid yields 1.55 g (92%) of IVi, mp. 166-168°(from ethanol).
Anal. Calcd. for $C_{18}H_{15}N_3O_4$: C, 64.09; H, 4.45; N, 12.46. Found C, 63.88; H, 4.50; N, 12.42.

IR (KBr pellet): 3320, 3260, 2250, 1685, 1600 cm^{-1}. NMR (DMSO-d_6): δ 8.85 (s, 1H, NH), 7.00-8.30 (m, 9H arom), 6.85 (s, 1H, OH), 4.55 (d, 1H), 3.90 (m, 1H), 2.20 (m, 2H, CH_2).

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